Modern Concepts of Cardiovascular Disease

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STRESS AND HEART DISEASE*

Stress, for the purpose of this discussion, is present when the adaptive mechanisms of the living organism, in this instance man, are taxed or strained. The results are by no means specific. In fact, the variability of response of the human being may be immense, varying from invention or artistic creation, on the one hand, to surrender or death on the other. Among the great variety of possible reactions to stressful circumstances are a host of alterations in visceral function, including the elements of the cardiovascular system.

Evidence that the highest neural centers are involved in cardiovascular phenomena has been available from time immemorial, since it has been observed that symbolic stimuli, that is, circumstances without intrinsic force but having a peculiar meaning for the individual concerned, were capable of arousing a multitude of cardiovascular responses, including changes in rate, rhythm and peripheral vascular function. Somehow, the potential importance of such changes escaped notice until they were produced experimentally with electrodes in the laboratory.

Vascular reactions subserved by neural mechanisms range from the altogether peripheral axon reflex through a variety of autonomic effector functions mediated via the spinal cord, and reflexes at the level of the brain stem brought about through afferents from various specialized receptors, such as osmoreceptors, baroreceptors, chemoreceptors, and others in the blood vessels and in the brain. These are sensitive to minor changes in the composition of the blood, especially to reductions in oxygen tension or alterations in blood pH. In many instances, it is known that the efferent impulses activated thereby may result in widespread and often disabling bodily changes.

Information as to precisely what circulatory patterns are subject to influence from the highest neural centers is still only fragmentary, but already impressive enough to indicate that the cerebral cortex must be considered along with the thyroid, the adrenal gland and the pituitary as potentially controlling cardiovascular responses in man. Rarely such changes are volitional, as they were in the case reported by McClure.[1] His patient was able to produce temporary cardiac arrest at will. In most instances, however, it would appear that the activity of the highest neural centers in governing the cardiovascular apparatus is part of unconscious neural processes and often, perhaps, as part of a general bodily adaptation to a challenging situation or circumstance. Very commonly, such experiences involve anticipation of some action requiring a change in cardiovascular dynamics or function.

Need for Increased Peripheral Flow

The hemodynamic changes appropriate to situations requiring an increased peripheral circulation, such as anemia, vitamin deficiencies, arteriovenous shunts and hyperthyroidism, include tachycardia and increased stroke volume with a lowering of peripheral resistance. It is well known that the same adjustments occur temporarily during vigorous muscular effort. They may also occur in anticipation of such an effort as before running a race. It is less clear, but an equally demonstrable fact, that precisely the same bodily reactions occur in the man who is driving his automobile and suddenly hears the shrill whirr of a motorcycle policeman's siren. He is not running or even planning to run, if he is wise, and yet his cardiovascular apparatus behaves as if he were running and as if his muscles

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needed added nourishment. Such "as if" reactions occurring unconsciously and in association with conscious or unconscious emotional conflicts have provided the subject of another communication.[2]

Need to Increase Pressure in the System

During blood loss, as in donors for transfusion, an increase has been observed in peripheral resistance without increased cardiac output but with the maintenance, or even elevation, of blood pressure. Such changes have also been seen to occur in subjects volunteering as transfusion donors but before venapuncture was carried out.[3] These changes, of course, are typical of those encountered in essential hypertension and they may also be seen as overcorrective responses following the injection of hypotensive drugs, or upon assuming the recumbent position after an episode of postural hypotension. Psychiatrists have for years pointed out that patients with essential hypertension are psychologically poised for combat but that the aggressive action is unconsciously and powerfully restrained. An ingenious experimental situation was set up by certain Russian workers at the primate station in Zukhumi.[4] Baboons who had become self-selected mates were separated. The female was placed in a large cage with a strange male. Her mate was placed alone in a smaller cage alongside. The workers observed that the cuckolded mate regularly developed sustained hypertension. There is insufficient evidence to conclude that essential hypertension occurs in a suitable susceptible subject as part of a cardiovascular adjustment, as if in preparation for combat with threatened blood loss. Nevertheless, the fact remains that the appropriate hemodynamic mechanisms are connected with, and capable of reacting to, neural connections in the interpretive areas of the brain.

Cardiac Arrest

There has been some difference of opinion among investigators as to whether such effects as "voodoo death" or sudden death in healthy individuals, as seen from time to time in our own culture, are attributable to massive sympathetic or parasympathetic discharges. Cannon took the former view, but more recently the experiments of Richter indicate that heart slowing as a result of vagal stimuli may be the important factor with the ultimate production of ventricular fibrillation.[5] Richter was able to produce such vagal effects experimentally in rats who were placed in a tank from which they could not escape and in which they were made to swim indefinitely. It is interesting that survival among these rats was greatly reduced when their orienting moustache hairs were cut off, thus putting them into an even more unaccustomed, "terrifying" and presumably hopeless situation. Richter further noted that wild rats did not survive this ordeal as well as did the domesticated rats, who had been accustomed over the generations to the arduous buffetings of the experimental laboratory. A comparable observation in a human being was made by W. Fuqua, who was on duty in a field hospital during the war in Korea (personal communication). He was examining a marine with symptoms of influenza and, after listening to the breath sounds with his stethoscope, Fuqua said "now stop breathing" as he began to listen to the heart. At that moment, there was heard a loud burst of enemy artillery fire. The marine's heart suddenly stopped; he remained in asystole for one minute and with no effective pulsation for at least two minutes. Further contributory evidence in human beings was gathered by R. H. Furman in the course of examining the hearts of soldiers at the time of induction into the military service (personal communication). The long line of recruits came for their cardiovascular examination immediately after a blood sampling syringe was withdrawn from their veins. He thus caught many subjects almost in the process of fainting and indeed caught some of them as they were falling to the floor. Prompt examination revealed pulse rates in the low 40's and blood pressure that was almost unobtainable. Although many recruits showed tachycardia, those who fainted uniformly displayed a vagal pattern.

Work of the Heart

Muscular effort is a familiar stimulus to cardiovascular function. On the basis of the predictability in degree and duration of changes evoked by measured amounts of exercise, various workers have devised tests of adequacy of cardiac function and of cardiac reserve.

Briefly, expected changes include temporary tachycardia and increase in the cardiac output with each beat (stroke volume), followed by return to resting levels at a rate depending upon the amount of exertion undertaken. In healthy subjects, changes in the pattern of the electrocardiogram do not ordinarily occur with exercise; when they do, they are thought to indicate a degree of cardiac insufficiency and a reduction of the reserve capacity of the heart.

Tests of exercise tolerance have been difficult to interpret because factors other than exercise are capable of inducing tachycardia, increase in stroke volume, and even T-wave changes in the electrocardiogram.[6] Prominent among such factors are life situations, either consciously or unconsciously threatening to the security of the individual. Situations of pleasurable anticipation may also be associated with tachycardia and an increase in stroke volume. It is as though bodily changes were occurring in preparation for exertion, e.g., fighting, running away, or active par-

ticipation in some pleasurable situation. When exercise is actually undertaken under such circumstances, the cardiovascular adaptation may be excessive or unduly prolonged during recovery, as though a much greater muscular effort had been anticipated.

The work of Wolf and Wolff,[7] and later of Hickam, et al.,[8] established that variations in stroke volume and cardiac output correspond with changes in life situation and emotional state. Duncan, et al.,[9] related them to some of the symptoms of neurocirculatory asthenia. The possible importance of such alterations in cardiac function to patients with already damaged hearts has not been assessed. It is noteworthy, however, that the work of the heart may be increased and its efficiency affected by circumstances constituting figurative burdens. It is evident that the work of the heart cannot be estimated with any degree of accuracy with reference to the amount of exertion actually undertaken. If the subject is "in training," cardiovascular efficiency will be such that a relatively great load may be carried on with a minimum of work. On the other hand, in training or not, the heart may be called up to work hard with the subject sitting or lying while contemplating, consciously or unconsciously, some troublesome personal problem.

Cardiac Rhythm. Arrhythmias, including paroxysmal atrial tachycardia, extrasystoles, atrial fibrillation, and even the more serious paroxysmal ventricular tachycardia may occur in association with troublesome events in the day-to-day experiences of individuals who have no other detectable evidence of heart disease. It would appear that this variety of disorders of cardiac rhythm may be precipitated by, or possibly fundamentally related to, threats arising out of the life situation. It is certainly unnecessary always to postulate underlying structural disease of the myocardium as a cause of arrhythmias, even in the case of such potentially serious disorders as atrial fibrillation and ventricular tachycardia.[3]

Electrocardiogram. Ordinarily, when there are changes in the pattern of the electrocardiogram during exercise, the assumption is made that there is a disturbance of cardiac nutrition. In the study of Stevenson, et al.,[10] 19 patients displayed changes in S-T segments or T waves to a degree considered significant, according to the criteria of Master, when exercise was performed during a period of stress. The same exercise on a day of relative security and relaxation produced less change in the electrocardiogram, or none at all. In all but one of the 19, it was possible to produce electrocardiographic changes during an interview covering pertinent personal problems and without exercise or conscious anticipation of muscular effort. This information

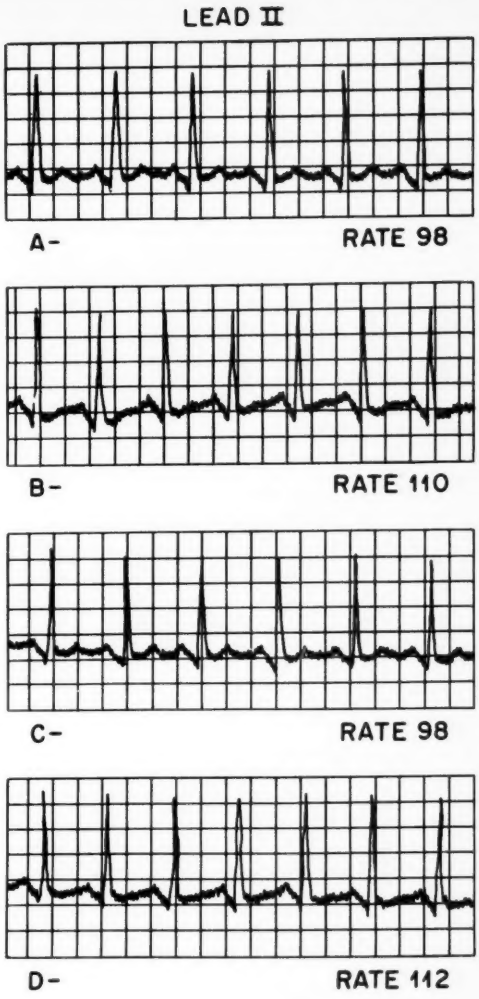

Figure 1. Electrocardiographic changes induced by exercise and during anxiety without exercise.

is in keeping with the general concept that man during stress may react with his cardiovascular apparatus as if he were about to engage in strenuous muscular activity without any actual awareness of anticipating exercise.

Figure 1 illustrates changes observed in the electrocardiogram of one subject, aged 32, who at the time had symptoms of palpitation and reduced exercise tolerance without evidence of struc-

tural heart disease except in the electrocardiogram; this was normal at rest but the T waves became inverted during exercise or during a stressful interview. Seven years later, the patient still showed no further evidence of heart disease.

The mechanisms responsible for these changes cannot be stated on the basis of the data at hand. They may include coronary ischemia or perhaps merely sympathetic stimulation. In any case, the electrocardiogram recorded during severe anxiety in a man with suspected coronary artery disease must be interpreted in the light of these findings. Although the changes may be quickly reversible and not always of such grave import as is ordinarily thought, the possibility that repeated or sustained situational stress may lead to irreversible changes must be taken into consideration in planning therapy.

Need for Available Lipids as Fuel for Strenuous Effort

It is easier to produce sustained hyperlipemia in man by starvation than by feeding. This may be due to the fact that there is a pressing need to conserve glucose during starvation because nervous tissues cannot metabolize other products. The muscles, however, and other bodily tissues, can use fat for fuel as readily as glucose. The mechanism responsible for lipid mobilization in this situation is not known. but the evidence of Seifter, et al.,[11] would implicate the pituitary. Fat must also be metabolized in preference to glucose during strenuous muscular effort. There is not sufficient glucose in the body, or in glycogen stores, to support the stoking of a furnace or a cross-country ski. Therefore, as in starvation, the muscles must rely on fat as a source of energy. Here again, as shown in the work of B. Balke and J. A. Green, there occurs an elevation in serum cholesterol and lipids (personal communication).

Numerous investigators have shown that stressful life experiences are also capable of evoking hypercholesterolemia. Several workers have studied the serum concentration of cholesterol and lipids in students before, during and after the stress of examinations. All of them, including Thomas and Murphy,[12] Wertlake, et al.,[13] Grundy and Griffin,[14] and Dreyfuss and Czaczkes,[15] found higher values during the stressful periods than otherwise. Dreyfuss also measured the clotting time and found it accelerated in 36 medical students the morning of a final examination in medicine. The studies of Groen,[16] Groover,[17] Friedman and Rosenman,[18] and Hammarsten, and associates,[19] have given evidence that the lipid regulating mechanisms are responsive to situational stresses. The latter studies were undertaken on 12 men ranging in age from 30 to 70. They all had well documented evidence of myocardial infarction. These individuals were followed at weekly intervals with chemical determination of serum cholesterol, lipid phosphorus and lipoproteins, as estimated by the ultracentrifugal technique. At the same time, each subject kept a written record of everything consumed each day at meals, and between meals. The dietary records were later analyzed and roughly quantitated in terms of caloric content and proportion of fat, carbohydrate and protein in the diet. In addition, the subjects were weighed each week and carefully interviewed concerning events of the week and their attitude and reactions to potentially stressful situations. Following the interview, the investigator recorded a judgment concerning the presence or absence of significant stress during the week and an estimate of its degree. These data were, of course, gathered and recorded entirely separately from the chemical measurements. Later correlation showed that unusually high cholesterol concentration, more than 15 per cent above the mean for any individual in the study, correlated with a high degree of significance with periods that had been separately judged as especially stressful. Similar correlation was found in the lipoproteins of the SF 0-12 and the SF 12-20 fractions. More recently, these data have been reinforced by studies of four subjects on balance regimens in a metabolic ward. During the period of rigidly maintained uniform diet and exercise, variations in the concentration of the serum cholesterol of 15 to 40 per cent were observed, amounting to nearly 100 mg. per cent. A high degree of statistical significance was noted when periods of cholestrol elevation were correlated with periods of separately judged emotional stress. Further documentation was available from short-term experiments in which the patients were subjected to stressful interviews concerning significant personal conflicts. In control interviews covering neutral topics, no elevations of serum cholesterol were observed. Following an hour of stressful discussion, however, an increase in the serum cholesterol was observed five out of six times.

The studies of Hammarsten, and his associates, indicated that patients with coronary artery disease were oriented to life along the line of effort, of doing things "the hard way." These patients placed an especially high value on doing things "on their own" and being solely responsible for their activities and experiences. Like Sisyphus, they appeared to be continually carrying a burden and never quite getting it to the top of the hill or the resting place. Moreover, the occurrence of coronary attacks appeared to correlate with periods when the individuals were carrying an especially heavy emotional load. It may be that the mechanisms that govern the concentration of serum lipid are brought into play in the face of demand for effort that is figurative as

well as literal. The possibility that any such changes are actually related to the mechanisms of coronary atherosclerosis is entirely speculative. Moreover, it should be borne in mind that not only are the mechanisms regulating the concentration of serum lipids and cholesterol unknown at present, but the significance of the relation of serum concentration of these substances to the integrity of arteries is equally obscure. Indeed, the extent to which the presence of atherosclerosis determines vascular accidents is also unknown.

The opinion of many present-day investigators is reflected in the following editorial comment of Oliver and Boyd in the *British Heart Journal:* "The remarkable social and economic changes of the century are undoubtedly stressful to some people. Increasing stress might favor the development of clinical coronary disease by disturbing normal endocrine balance and thus influencing both cholesterol metabolism and the coagulation and fibrinolytic systems. Similarly, long, continued environmental stress might disturb the autonomic control of the coronary arteries." [20] Convincing evidence to support such notions is still lacking, but several clinical studies of groups of patients with coronary artery disease would tend to support them. Thus, Friedman and Rosenman found higher serum cholesterol concentrations, a far greater incidence of arcus senilis and a vastly increased incidence of evidence of coronary artery diseases in subjects classified as oriented toward competitive activities with deadlines, as compared with anxious but noncompetitive people or with more passive subjects.[21] Russek reported similar findings among coronary patients,[22] and Dreyfuss [23] and Weiss, et al.,[24] observed special situational stresses as antecedent events to episodes of coronary occlusion.

Much of the confusion concerning the role of life stress in disease derives from failure to distinguish between cause and mechanism. All mechanisms are perforce organic and at the same time functional, since they involve the function of units of the body's equipment. Causes, on the other hand, are likely to derive from the outside, often from noxious stimuli in the environment. The causes, which may be multiple, activate the pathogenic mechanisms and produce bodily disorders and diseases. The ability of symbolic stresses to participate in the activation of disease mechanisms depends upon the fact that most bodily organs are connected with, and responsive to, impulses reaching them via autonomic and endocrine pathways, from the highest integrative centers of the nervous system, the interpretative areas of the brain.

The characteristics of a situation acting as a stimulus may activate, but do not determine, the nature of the response. The response will depend upon the state of the organism at the time of stimulation and on the organism's inherent characteristics. Thus, a precisely similar situation may have entirely different effects on two individuals or on the same individual at different times. The determinants include genetic equipment and other inherent characteristics of the individual which may be acquired. Thus, the effect of the stimulus must depend heavily on the prevailing state of the organism. The pertinence of the stimulus as a determinant of the pattern of response derives simply from the fact that it is the most recent event. Neither can one explain the phenomena observed in response to a symbolic stimulus in terms of the degree of emotional vulnerability of a particular subject, or in terms of nervous imbalance. As obtains with respect to exposure to infectious agents, it can simply be said that some people adapt more smoothly and effectively than others and thus remain healthier.

The evidence relating psychological phenomena to disease of the heart and blood vessels is fragmentary and at this stage altogether unconvincing. It is sufficiently promising, however, to warrant a great deal more systematic study and serious interest on the part of physiologists and clinicians.

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